



Cost-Effectiveness of iGlarLixi Versus Premix BIAsp 30 in People with Type 2 Diabetes Suboptimally Controlled by Basal Insulin in the US

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ABSTRACT

Introduction: Many people with type 2 diabetes mellitus (T2DM) experience suboptimal glycemic control and require therapy advancement. This cost-effectiveness analysis was conducted to compare iGlarLixi (insulin glargine 100 U/mL plus lixisenatide) versus BIAsp 30 (biphasic insulin aspart 30) in people with T2DM suboptimally controlled with basal insulin.

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Methods: The IQVIA Core Diabetes Model was used to estimate lifetime costs and outcomes for people with T2DM from a US healthcare payer perspective. Initial clinical data were based on the phase 3 randomized, open-label, active-controlled SoliMix clinical study, which compared the efficacy and safety of once-daily iGlarLixi with twice-daily BIAsp 30. Lifetime costs (US\$) and quality-adjusted life-years (QALYs) were predicted, and the incremental cost-effectiveness ratio (ICER) for iGlarLixi versus BIAsp 30 was estimated; the willingness-to-pay threshold was considered to be \$50,000. A subgroup analysis considered people with T2DM aged ≥ 65 years.

Results: Estimated QALYs gained were slightly higher with iGlarLixi compared with BIAsp 30 (9.3 vs. 9.2), with lower costs for iGlarLixi (\$117,854 vs. \$120,109); the ICER for iGlarLixi was therefore considered dominant over BIAsp 30 in the base case. Key drivers for cost savings were the higher dose and twice-daily administration for BIAsp 30 versus once-daily administration for iGlarLixi. The robustness of the base-case results was confirmed by sensitivity and scenario analyses. Results were similar in a subgroup of people with T2DM aged ≥ 65 years.

Conclusion: In people with T2DM with suboptimal glycemic control on basal insulin, iGlarLixi confers improved QALYs and reduced costs compared with BIAsp 30.

Keywords: BIAsp 30; Cost-effectiveness; Cost-utility; iGlarLixi; Older adults; Premix; SoliMix trial; Type 2 diabetes; United States

Key Summary Points

Why carry out this study?

Premix insulins (including biphasic insulin aspart 30 [BIAsp 30]) are recommended for the treatment of people with type 2 diabetes mellitus (T2DM) requiring therapy advancement, but are associated with increased risk of hypoglycemia and weight gain compared with combinations of basal insulin (BI) plus glucagon-like peptide-1 receptor agonists (such as insulin glargine 100 U/mL and lixisenatide [iGlarLixi]).

The efficacy and safety of once-daily iGlarLixi compared with twice-daily premix BIAsp 30 in people with T2DM suboptimally controlled on BI was demonstrated in the randomized phase 3 SoliMix trial.

In this comprehensive economic analysis we estimated the lifetime cost-effectiveness of iGlarLixi from a US healthcare payer perspective, compared with BIAsp 30.

What was learned from this study?

Estimated quality-adjusted life-years (QALYs) gained were slightly higher with iGlarLixi versus BIAsp 30 (9.3 vs. 9.2), with lower costs for iGlarLixi (\$117,854 vs. \$120,109); iGlarLixi was considered dominant over BIAsp 30 in the base case, with similar results in a subgroup of individuals aged ≥ 65 years.

In people with T2DM with suboptimal glycemic control on basal insulin, iGlarLixi confers slightly increased QALYs and reduced costs compared with BIAsp 30.

INTRODUCTION

Diabetes continues to be a major global health threat and its burden is expected to increase in the coming decades. The worldwide prevalence of diabetes is predicted to increase from 8.8% in 2015 to 10–12% by 2030 [1]. There are over 37 million people in the USA living with diabetes, of whom approximately 90–95% have type 2 diabetes mellitus (T2DM) [2]. It has been estimated that 29.2% of US adults aged ≥ 65 years have diabetes, representing the age group with the highest diabetes prevalence [3]. In 2021, diabetes was associated with \$966 billion in health expenditure costs in the USA, reflecting an increase of 316% over the preceding 15 years [4]. Clinical management of people with T2DM represents a major public health challenge and a pressing economic burden for healthcare systems in the USA. People with T2DM who are aged ≥ 65 years have a higher risk of hypoglycemia and postprandial hypoglycemia than younger T2DM populations and, consequently, have different considerations for management of age-related cardiovascular risk factors [5].

Many people with T2DM are suboptimally controlled on basal insulin (BI) analogs and often require therapy advancement with dual or triple therapy [6, 7]. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend four therapeutic escalation approaches, including the addition of a rapid-acting insulin, multiple daily premix insulin doses (basal and prandial insulin co-formulation) or a daily or weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) to the existing BI regimen, or a switch to a once-daily fixed-ratio combination of BI and GLP-1 RA [6, 7]. Fixed-ratio combination products have been developed to facilitate administration of effective glucose-lowering agents compared with the co-administration of individual agents.

Premixed insulin doses (rapid- and intermediate-acting insulin co-formulations) are among the recommended therapeutic options in people with T2DM requiring therapy advancement [7, 8]. However, premixed insulin has been shown to increase the risks of hypoglycemia

and weight gain, in addition to requiring multiple daily injections, frequent glucose monitoring and regimented lifestyles (such as eating meals at a consistent time), which may increase treatment burden and reduce adherence [9–11].

The fixed-ratio combination of the long-acting BI analog insulin glargine 100 U/mL and the GLP-1 RA lixisenatide, iGlarLixi, is approved in the USA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM [12]. The SoliMix study (EudraCT: 2017-003370-13), a phase 3, randomized, open-label, active-controlled study over 26 weeks, compared once-daily iGlarLixi with twice-daily premix biphasic insulin aspart 30 (BIAsp 30) in people with T2DM who were suboptimally controlled on BI and required therapy advancement. Results from the SoliMix study demonstrated that iGlarLixi provided statistically significant improvements in glycemic control, body-weight and hypoglycemia, with a preference for iGlarLixi expressed by study participants. Therefore, iGlarLixi represents an efficacious, simple, well-tolerated and preferred alternative to BIAsp 30 in people with T2DM who require therapy advancement [13, 14].

In line with increasing pressure on healthcare budgets, using cost-effectiveness analyses to inform the choice of therapeutic interventions is of growing importance. This comprehensive economic analysis, therefore, aimed to estimate the lifetime cost-effectiveness of iGlarLixi from a US healthcare payer perspective, compared with BIAsp 30.

METHODS

Study Overview

The IQVIA Core Diabetes Model (CDM) version 9.5, which is an extensively validated and widely applied non-product-specific cohort simulation model, was used to estimate the lifetime cost-effectiveness of once-daily iGlarLixi versus twice-daily BIAsp 30 [15–17]. The CDM predicts disease progression through a series of inter-dependent Markov sub-models that simulate the progression of disease-related complications using a set of equations for

progression of the disease risk factors (United Kingdom Prospective Diabetes Study [UKPDS] Outcomes Model no. 68 [UKPDS 68] and clinical tables) [18] and for predicting cardiovascular and mortality risk (Framingham equation and UKPDS 82, respectively) [19]. This cost-effectiveness analysis assumed a conservative willingness-to-pay (WTP) threshold of US\$50,000 per quality-adjusted life-year (QALY) and an annual discount rate of 3% for both cost and outcomes [20]. A hypothetical cohort of 1000 adults was simulated in 1000 model iterations over a lifetime time horizon. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Model Inputs and Structure

The clinical population for this model was people with T2DM who had suboptimal glycemic control with BI plus oral antidiabetic drugs (metformin with or without sodium-glucose co-transporter-2 inhibitor [SGLT2i]). Baseline characteristics (Table 1), baseline complications and duration of diabetes were sourced from the SoliMix clinical trial [13]. For baseline values that were not collected in the SoliMix trial, population averages based on published literature [16] or data from the Lixilan-L trial [21] were used. Model participants were assumed to enter the model with a glycated hemoglobin (HbA1c) level of 8.6%; relative treatment effects on HbA1c, body mass index (BMI) and hypoglycemia over the first year were applied, based on observations from the SoliMix trial (Table 2).

After the first year, progression of HbA1c was assumed to increase by 0.15% annually in the base-case analysis, while the relative treatment effect on BMI was assumed to be maintained until rescue therapy was received. The use of iGlarLixi resulted in a BMI decrease, whereas the use of BIAsp 30 resulted in a BMI increase. Once HbA1c returned to the baseline value of 8.6%, switch to rescue therapy was assumed, consisting of one shot of rapid-acting insulin in addition to BI (basal plus regimen) for both

Table 1 Baseline characteristics

Variable	Mean (SD)	References
<i>Demographics</i>		
Start age (years)	59.80 (10.20)	SoliMix trial [13]
Duration of diabetes (years)	13.00 (7.20)	
Proportion male	0.498	
<i>Baseline risk factors</i>		
HbA1c (%)	8.60 (0.70)	SoliMix trial [13]
Systolic blood pressure (mmHg)	131.70 (13.70)	
Diastolic blood pressure (mmHg)	77.80 (8.60)	
Total cholesterol (mg/dL)	180.52 (44.76)	Aroda et al. [21] ^a
High-density lipoprotein (mg/dL)	50.62 (13.18)	
Low-density lipoprotein (mg/dL)	100.55 (37.79)	
Triglycerides (mg/dL)	149.13 (98.39)	
Body mass index (kg/m ²)	29.90 (4.90)	SoliMix trial [13]
Estimated glomerular filtration rate (mL/min/1.73 m ²)	86.10 (23.56)	
Hemoglobin (g/dL)	13.90 (1.5)	
White blood cells (10 ⁶ /mL)	7.55 (1.86)	
Heart rate (bpm)	77.00 (9.00)	
Waist-to-hip ratio	0.93	CDM default
Urinary albumin to creatinine ratio	3.10	

Table 1 continued

Variable	Mean (SD)	References
Serum creatinine (mg/dL)	0.85 (0.21)	SoliMix trial [13]
Serum albumin (g/dL)	3.90	CDM default
Waist circumference (cm)	87.84	
Proportion smoker	0.116	SoliMix trial [13]
Cigarettes/day	13.20	
Alcohol consumption (oz/week)	92.01	
<i>Racial characteristics</i>		
Proportion White	0.630	SoliMix trial [13]
Proportion Black	0.002	
Proportion Hispanic	0.00	
Proportion Native American	0.017	
Proportion Asian/Pacific Islander	0.351	
<i>Baseline CVD complications</i>		
Proportion myocardial infarction	0.027	SoliMix trial [13]
Proportion angina	0.041	
Proportion peripheral vascular disease	0.006	
Proportion stroke	0.020	
Proportion heart failure	0.021	
Proportion atrial fibrillation	0.016	
Proportion left ventricular hypertrophy	0.001	
<i>Baseline renal complications</i>		
Proportion microalbuminuria	0.001	SoliMix trial [13]
Proportion macroalbuminuria	0.000	
Proportion end-stage renal disease	0.000	

Table 1 continued

Variable	Mean (SD)	References
<i>Baseline retinopathy complications</i>		
Proportion background diabetic retinopathy	0.151	SoliMix trial [13]
Proportion proliferative diabetic retinopathy	0.142	
Proportion severe vision loss	0.006	
<i>Baseline macular edema</i>		
Proportion macular edema	0.00	SoliMix trial [13]
<i>Baseline cataract</i>		
Proportion cataract	0.05	SoliMix trial [13]
<i>Baseline foot ulcer complications</i>		
Proportion ulcer	0.001	SoliMix trial [13]
Proportion history of amputation	0.001	
<i>Baseline neuropathy</i>		
Proportion neuropathy	0.277	SoliMix trial [13]
Proportion depression	0.026	

bpm beats per min, *CDM CORE* Diabetes Model, *HbA1c* glycated hemoglobin, *oz* ounce (Imperial unit), *SD* standard deviation

^aData on cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides were not collected in the SoliMix trial; therefore, baseline values for these variables were taken from the LixiLan-L trial [21]

treatment arms. Treatment effects for rescue therapy (effects on HbA1c, BMI and hypoglycemia rates) were taken from the GetGoal Duo-2 study [22]. Mortality rates were predicted using UKPDS 82 risk equations. Utility values were derived from published literature (see the Electronic Supplementary Material [ESM] Table S1). A “minimum” approach was used to estimate utilities in all model simulations, whereby the lowest-state utility associated with existing comorbidities was used and event

Table 2 Treatment effects used in the base-case analysis

Treatment effect	iGlarLixi	BIAsp 30
LSM change in HbA1c from baseline, % (SE)	−1.30 (0.06)	−1.05 (0.06)
LSM change in BMI from baseline, kg/m ² (SE)	−0.20 (1.10)	0.50 (1.10)
Non-severe hypoglycemia events (per 100 patient-years) ^a	245	348
Severe hypoglycemia events (per 100 patient-years)	0.5	1

BIAsp 30 biphasic insulin aspart 30, *BMI* body mass index, *iGlarLixi* insulin glargine 100 U/mL plus lixisenatide, *LSM* least squares mean, *SE* standard error

^aHypoglycemia ≤ 70 mg/dL (≤ 3.9 mmol/L)

disutilities for subsequent events occurring in that year were added, resulting in an annual utility score for each simulated person in the model.

Cost Inputs and Assumptions

Direct medical costs—comprising acquisition costs, management costs (screening test, concomitant medication) and costs of T2DM complications (cardiovascular complications, renal complications, acute events, eye disease, neuropathy, foot ulcer and amputation) reported in 2021 US\$—were derived using published values for wholesale acquisition costs for treatments or from a combination of published literature and Medicare fee schedules for complications and events (ESM Tables S2, S3). Self-monitoring of blood glucose occurred once per day for iGlarLixi and twice daily for premix BIAsp 30, in line with the SoliMix study design. The maximum recommended dose of metformin (1500 mg per day) was applied equally between both arms. In the USA, iGlarLixi is available as 100 U/mL insulin glargine + 33 µ/mL lixisenatide. Treatment costs for both iGlarLixi and BIAsp 30 were applied until rescue therapy, and then the same costs for rescue therapy were applied to both study arms. Drug acquisition cost was

calculated using the dose observed in the SoliMix trial up to 26 weeks. From 26 weeks until administration of rescue therapy, the average dose used at the end of the SoliMix study (40 units) was applied.

Analyses

In the base-case analysis, costs and QALYs were obtained for iGlarLixi and BIAsp 30; incremental differences in costs and QALYs and incremental cost-effectiveness ratio (ICER) estimates were calculated for iGlarLixi relative to BIAsp 30. A subgroup analysis was also performed in people with T2DM aged ≥ 65 years. Baseline characteristics and treatment effects for this population are presented in the ESM (ESM Tables S4, S5). Scenario analyses were conducted to evaluate the impact of parameter uncertainties on the conclusion, including variations in discounting, HbA1c progression, disability for non-severe hypoglycemic event and iGlarLixi and BIAsp 30 prices (ESM Table S6). A probabilistic sensitivity analysis (PSA) was also conducted to evaluate uncertainty in the model by random variation of key parameter inputs within plausible distributions. Probabilistic distribution of key transition probabilities (myocardial infarction, stroke, congestive heart failure and angina) were applied by bootstrap sampling around the 95% confidence interval of the regression coefficient. For utilities and treatment effects, mean and standard error values were used to generate random sampling within a beta-distribution function. Direct costs (excluding acquisition costs, which were assumed to be fixed) were randomly sampled based on log-normal distribution within a 20% variance.

RESULTS

Base-Case Analysis

In the base-case analysis, treatment with iGlarLixi was associated with lower costs and slightly increased QALYs compared with BIAsp 30, equivalent to cost savings of US\$2255 and 0.138

Table 3 Cost-effectiveness results (base-case analysis) for iGlarLixi versus BIAsp 30

Cost-effectiveness results	iGlarLixi	BIAsp 30
<i>Base-case analysis</i>		
QALY, year	9.333	9.195
Total cost, US\$	117,853	120,109
Incremental QALY, year	0.138	
Incremental costs, US\$	−2255.00	
ICER, US\$ per QALY gained	Dominant	
<i>Older (aged ≥ 65 years) subgroup analysis</i>		
QALY, year	6.658	6.569
Total cost, US\$	93,109.86	96,131.32
Incremental QALY, year	0.09	
Incremental costs, US\$	−3021.46	
ICER, US\$ per QALY gained	Dominant	

ICER Incremental cost-effectiveness ratio, QALY quality-adjusted life-year

QALYs gain (Table 3; Fig. 1a); iGlarLixi was therefore considered dominant versus BIAsp 30 (i.e. was more effective and less costly). Patients receiving iGlarLixi and BIAsp 30 switched to rescue therapy after year 6 and year 5, respectively (Fig. 2a). An initial decline in BMI was observed for patients treated with iGlarLixi, while patients receiving BiAsp 30 experienced an increase in BMI, which increased further after switching to rescue therapy (Fig. 2b). Cumulative incidence per 1000 patient-years of non-severe hypoglycemic events was lower for iGlarLixi (37.04) compared with premix BIAsp 30 (42.17) and was similar for severe hypoglycemia incidence (0.08 vs. 0.13, respectively). The key drivers for cost savings with iGlarLixi were a higher dose and twice-daily administration for BIAsp 30 compared with once-daily administration for iGlarLixi. The key drivers for the gain in QALYs for iGlarLixi were the reduction in HbA1c levels, weight loss and fewer hypoglycemic events (Fig. 2; ESM Table S3).

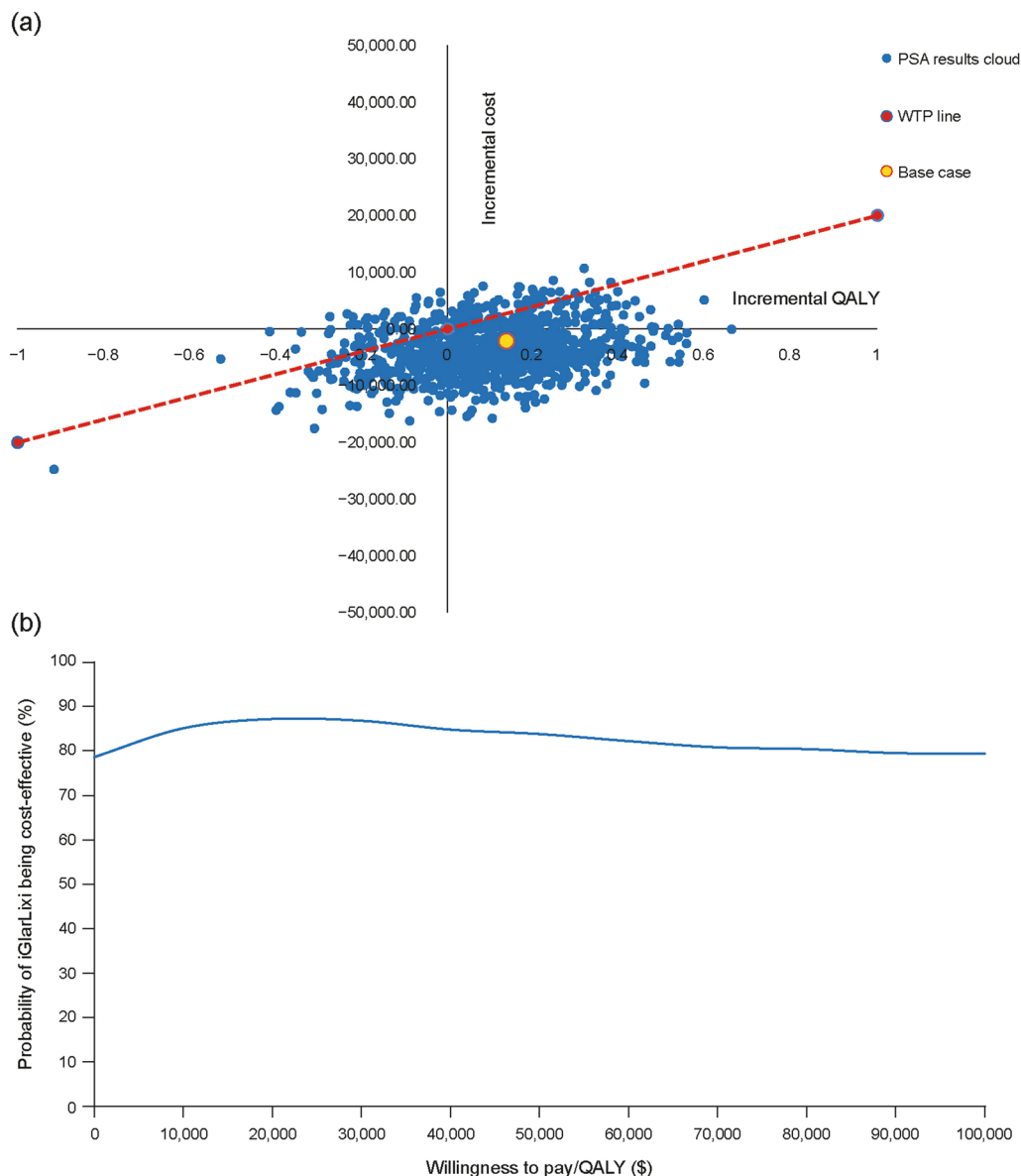


Fig. 1 Base-case cost-effectiveness planes (a) and cost-effectiveness acceptability curves (b) for iGlarLixi versus BIAsp 30. *BIAsp 30* Biphasic insulin aspart 30, *iGlarLixi*

insulin glargine 100 U/mL plus lixisenatide, *PSA* probabilistic sensitivity analysis, *QALY* quality-adjusted life-year, *WTP* willingness-to-pay

Subgroup and Scenario Analyses

A subgroup analysis was conducted to assess cost-effectiveness in people aged ≥ 65 years (Table 3). iGlarLixi was associated with lower costs and more QALYs compared with BIAsp 30, equivalent to cost savings of US\$3021 and 0.09 QALYs gain. Multiple scenario analyses assessed

the robustness of the base-case model assumptions (ESM Table S7). In extensive scenario analyses, iGlarLixi was dominant in eight of ten scenarios tested. In one scenario (discounting insulin products), iGlarLixi was considered not cost-effective at a WTP threshold of US\$50,000 per QALY gained; in scenario-testing the switch to rescue therapy when HbA1c reached 7.5%

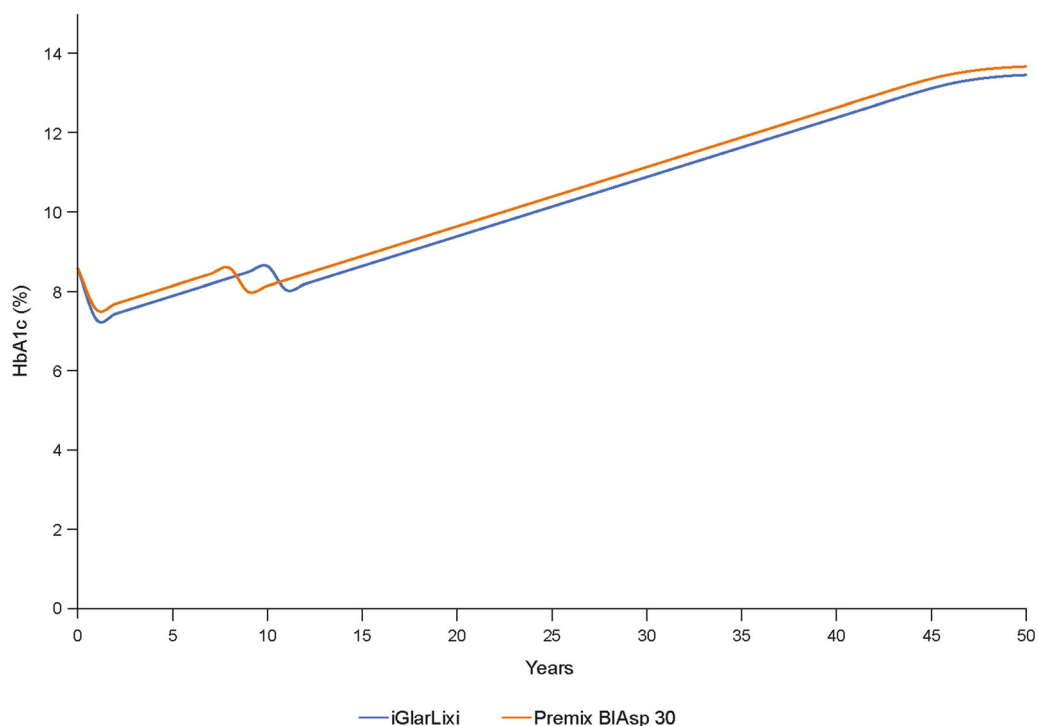


Fig. 2 Progression of HbA1c over the time of the base-case analysis. *HbA1c* Glycated hemoglobin

instead of 8.6%, iGlarLixi was not considered to be cost-effective.

Probabilistic Sensitivity Analysis

The PSA results showed that for 53% of the iterations, the ICER for iGlarLixi lay in the southeast quadrant, indicating lower costs and increased QALYs gained compared with BIAsp 30 (Fig. 1a). At a WTP threshold of US\$50,000 per QALY, iGlarLixi was cost-effective in > 80% of cases (Fig. 1b).

DISCUSSION

This study evaluated the cost-effectiveness of iGlarLixi versus BIAsp 30 and demonstrated that iGlarLixi is associated with slightly more QALYs gained (mainly driven by lower incidence of hypoglycemia) and with reduced HbA1c and BMI in people suboptimally controlled on BI. iGlarLixi was also associated with lower costs resulting from differences in dose-related offset costs; the total insulin dose at the

end of the SoliMix study was considerably lower for iGlarLixi than for BIAsp 30 (40 units vs. 58 units, respectively) [13]. iGlarLixi was considered dominant and can therefore be considered a cost-effective alternative to BIAsp 30 in the USA. Similar results were found for the older subgroup analysis. Extensive scenario analyses and PSA consistently supported the base-case findings, demonstrating the robustness of these outcomes. In a scenario analysis evaluating a lower HbA1c threshold for administration of rescue therapy (7.5% instead of 8.6%), iGlarLixi was not deemed to be cost-effective. This is because lower efficacy with BIAsp 30 leads to the threshold for administration of rescue therapy being reached much sooner (after 1 year, compared with after 3 years in the iGlarLixi arm) and a consequent reduction in treatment costs in the BIAsp 30 arm.

Observational studies have previously reported poor outcomes with premixed insulin in real-world practice, with relatively few people achieving glycemic target within 12–24 months of initiating therapy [23, 24]. These poor outcomes are likely to be at least partially

attributable to issues relating to adherence and persistence [11, 25]. The current model assumes durable and predictable treatment effects and does not consider the impact of adherence and persistence to therapy. However, given the reduced injection burden (once daily vs. twice daily) and statistically significant superior glycemic control, and the body-weight outcomes and lower hypoglycemia incidence observed with iGlarLixi compared with BIAsp 30, it may be reasonable to hypothesize that adherence is more likely to be an issue with BIAsp 30. In support of this, patient-reported outcomes (including the Treatment-Related Impact Measure Diabetes) indicated a preference for iGlarLixi over BIAsp 30 in the SoliMix trial [14]. This assumption is further supported by the higher persistence with iGlarLixi compared with basal insulin and premixed insulins demonstrated in the SoliComplex real-world study [26, 27].

A previous publication reported cost-effectiveness estimates for people receiving iGlarLixi in the post-BI setting and found that iGlarLixi was cost-effective compared with other insulin and GLP-1 RA combination regimens (insulin glargine plus dulaglutide, insulin glargine plus liraglutide and insulin degludec plus liraglutide) [28]. Clinical outcomes over the model time horizon were estimated to be comparable between regimens, but iGlarLixi was associated with substantial cost savings.

Limitations

This analysis was performed utilizing US metrics, and this should therefore be considered when extrapolating the findings to other markets and currencies. The data used in the analysis to predict long-term outcomes were relatively short-term (26 weeks from the SoliMix trial); however, the robustness of the results was confirmed with sensitivity and scenario analyses. In our analysis, identical rescue-therapy regimens were assumed for both treatment arms. However, it could be hypothesized that people receiving BIAsp 30 in real-world clinical practice may be more likely to receive additional GLP-1 RA or SGLT2i as part of their rescue-therapy regimen. This would be likely to

increase the cost of BIAsp 30 relative to iGlarLixi. In relation to the subgroup analysis of persons aged ≥ 65 years, it was not assessed how enrollment in the Part D Senior Savings Model for Medicare beneficiaries would impact cost-effectiveness. Furthermore, progression of disease risk factors was based on UKPDS 82 risk equations, which are widely used in diabetes simulation models [29–33], but the UKPDS trial population might not be representative of current clinical practice in the USA. Lastly, an acknowledged limitation of cost-effectiveness analyses applying trial data is that treatment outcomes with iGlarLixi or BIAsp 30 in real-world clinical practice may differ due the regular monitoring of participants in a clinical trial during the study period; for example, the incidence of severe hypoglycemia is assumed to be lower compared with routine clinical practice due to the aforementioned rigorous monitoring and follow-up in trials. In the SoliMix trial, severe hypoglycemia rates were relatively low compared with clinical settings, which may lead to an underestimation of the impact of severe hypoglycemia, in particular in the subgroup of ≥ 65 year olds.

CONCLUSION

In conclusion, iGlarLixi was associated with improved clinical outcomes at lower costs relative to BIAsp 30 in people with T2DM suboptimally controlled on BI. At a WTP threshold of US\$50,000 per QALY gained, iGlarLixi was cost-effective versus BIAsp 30 from a US healthcare payer perspective.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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